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Original article

Recombinant human erythropoietin in the treatment of chemotherapy-induced anemia and prevention of transfusion requirement associated with solid tumors: A randomized, controlled study

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Summary

Background: Anemia is a common side effect of anticancer chemotherapy. Blood transfusion, previously the only available treatment for chemotherapy-induced anemia, may result in some clinical or subclinical adverse effects in the recipients.

Recombinant human erythropoietin (rhEPO) provides a new treatment modality for chemotherapy-induced anemia.

Patients and methods: To evaluate the effect of rhEPO on the need for blood transfusions and on hemoglobin (Hb) concentrations, 227 patients with solid tumors and chemotherapy-induced anemia were enrolled in a randomized, controlled, clinical trial. Of 189 patients evaluable for efficacy, 101 received 5000 IU rhEPO daily s.c., while 88 patients received no treatment during the 12-week controlled phase of the study.

Results: The results demonstrate a statistically significant reduction in the need for blood transfusions (28% vs. 42%, $P = 0.028$) and in the mean volume of packed red blood cells transfused (152 ml vs. 190 ml, $P = 0.044$) in patients treated with rhEPO compared to untreated controls. This effect was even more pronounced in patients receiving platinum-based chemotherapy (26% vs. 45%, $P = 0.038$).

During the controlled treatment phase, the median Hb values increased in the rhEPO patients while remaining unchanged in the control group. The response was seen in all tumor types.

Conclusions: RhEPO administration at a dose of 5000 IU daily s.c. increases hemoglobin levels and reduces transfusion requirements in chemotherapy-induced anemia, especially during platinum-based chemotherapy.

Key words: anemia, chemotherapy, malignancy, recombinant human erythropoietin

Introduction

In many cancer patients, anemia is a consequence of the malignant disease process itself. Cancer-related anemia is associated with excessive release of cytokines such as interleukin-1, tumor necrosis factor and interferons [1]. These immunomodulatory peptides interfere with endogenous erythropoietin (EPO) production and inhibit erythroid bone marrow production [2].

Myelosuppressive chemotherapy can exacerbate the development and progression of anemia in patients with malignant disease. Depending on the cytotoxic agents used and their cumulative doses, the incidence of transfusion-dependent anemia induced by platinum-containing chemotherapy ranges from 9% to 40% [3].

Anemia related to platinum-containing chemotherapy may be associated with two different mechanisms. Cisplatin impairs erythropoiesis by a direct toxic effect on renal erythropoietin-producing cells, resulting in inappropriate EPO levels relative to the degree of anemia [4, 5]. In addition, platinum-based chemotherapy suppresses erythroid progenitor cells in the bone marrow, an effect that is more prominent with carboplatin than with cisplatin [6].

The clinical symptoms in patients with malignant diseases and anemia range from fatigue and lethargy to dyspnea and cardiovascular effects as well as a reduced capacity for physical activity. Chemotherapy, radiotherapy or surgical treatment may be less well tolerated in the presence of anemia.

Many patients with chemotherapy-induced anemia require regular transfusions. Complications of tranfu-

sions, such as transmitted infections and immune or intolerance reactions, are rare, but they can have serious consequences [7]. Although in most European countries blood transfusions can be given on an outpatient basis, for many patients the application is associated with hospitalization.

Recombinant human erythropoietin (rhEPO) has been accepted as the standard treatment for anemia of chronic renal failure [8, 9], and phase I–II clinical studies have shown that rhEPO can ameliorate chronic and chemotherapy-induced anemia and reduce the need for transfusions in patients with various malignant diseases [6, 10–15].

The aim of this study was to consolidate data on the efficacy of rhEPO in patients with solid tumors and to identify subgroups of patients that exhibit the most pronounced benefit in order to optimize the use of this therapy in cancer patient populations.

Patients and methods

Patients

This study was approved by the local Ethics Committees, and carried out in accordance with the Helsinki Declaration All patients enrolled gave their informed consent.

Patients were eligible for the study if the following inclusion criteria were fulfilled: 1) adult patients (age $\geq$ 18 years) undergoing chemotherapy for solid malignant tumors with histologically and/or cytologically proven diagnoses; 2) anemia with hemoglobin (Hb) concentration $\leq$ 11 g/dl before first rhEPO administration; 3) Hb concentration $\leq$ 13.5 g/dl before first rhEPO administration, and drop in Hb concentration by at least 1.5 g/dl during the preceding chemotherapy cycle; 4) and had had at least one blood transfusion during the preceding chemotherapy cycle.

The following major exclusion criteria were adopted: 1) significant organ dysfunction not secondary to malignancy; 2) therapy-resistant hypertension; 3) thrombocytosis > 500,000/µl; 4) iron deficiency or other remediable causes of anemia (e.g., renal insufficiency); 5) epilepsy; 6) acute infection; 7) acute or chronic bleeding.

Study design

The study was implemented as an open, randomized, controlled, parallel-group study (controlled treatment phased out over 12 weeks). After the controlled treatment phase all patients received treatment with rhEPO, within an uncontrolled treatment phase over 12 weeks (results not included). RhEPO was administered at a dose of 5000 IU daily s.c., corresponding to approx. 450 IU/kg and week. The rhEPO was provided as epoetin beta by Boehringer Mannheim GmbH (Mannheim, Germany).

The primary variable of efficacy was the volume of packed red blood cells (PRBC) transfused during four-week intervals (i.e., weeks 1–4, 5–8, and 9–12) in the controlled treatment phase. In addition, the proportion of patients with transfusions and the transfusion-free time were analyzed. A secondary variable was the proportion of patients with response to treatment defined as a Hb increase $\geq$ 2 g·dl compared with baseline in a four-week interval during the controlled treatment phase, maintained without transfusions in that period or the previous four weeks. The time required until the first response to treatment was also analyzed.

Hematology was measured weekly, whereas biochemistry and iron metabolism parameters were determined every four weeks.

The safety of the rh-EPO treatment was assessed using spontaneously reported adverse events and safety laboratory variables. Anti-EPO antibodies were measured at baseline and at the end of the controlled treatment phase Endogenous erythropoietin levels were measured within three to seven days before the start of erythropoietin administration. No further measurements were made during the controlled treatment phase.

Statistical methods

Sample size was calculated for this trial to allow for 90% power to detect a difference in the volume of PRBC transfused per four weeks between the two treatment groups at a significance level of 5%. The resulting planned sample size was to enroll 300 patients with an aim of accruing 86 evaluable patients in each group completing the controlled treatment phase.

Wilcoxon's rank-sum test was used to compare the two groups with respect to the primary efficacy variable (transfusion volume required per four weeks). The number and percentage of patients with transfusion was calculated for the various four-week intervals (weeks 1–4, 5–8, and 9–12). The time to first transfusion and time to response were analyzed by the Kaplan–Meier method and the log-rank test, whereby a withdrawal due to death, adverse event, or non-response was considered non-response rather than censored. The influence of various factors on transfusion need and time to response was also evaluated. The following factors were considered: type of tumor, platinum-containing *versus* non-platinum-containing chemotherapy, platelet counts ($\leq 150 \times 10^9$/l vs. $> 150 \times 10^9$/l), distant metastasis (yes, no, not assessable), previous blood transfusions (yes vs. no), gender, serum EPO level at baseline ($\leq$ 50 mU/ml vs. > 50 mU/ml), ratio of observed vs predicted serum EPO level at baseline (O/P ratio) according to Beguin [15] ($\leq$ 0.9 vs. > 0 9), transferrin saturation ($\leq$ 20% vs. > 20%), and location of investigation (Germany, Italy, France, and other countries).

Results

Study population

Two hundred twenty-seven patients were randomized to treatment with rhEPO (n = 117) or to the control group (n = 110). Two hundred eighteen patients (rhEPO: n = 114; control: n = 104) started with the controlled treatment phase. Sixty-two patients in the control group and 75 patients in the rhEPO group completed the controlled phase of the study. Tumor progression, discontinuation of chemotherapy, and personal reasons were the most numerous causes of patient withdrawal in both groups. One hundred eighty-nine patients were evaluable for efficacy (101 in the rhEPO group and 88 in the control group), and 218 patients were evaluated for safety (114 in the rhEPO group and 104 in the control group). Characteristics of the patients included in the efficacy evaluation are described in Table 1.

The most common cancer was ovarian (n = 50), followed by breast and lung cancers. The prevalence of distant metastasis was 43% in both treatment groups.

The proportion of patients with bone metastasis, which may influence hematopoietic capacity, was similar within the group of rhEPO-treated and controlled patients (11% vs. 10%).

Fifty-seven patients (65%) in the control group and 58 (57%) in the rhEPO group had received chemotherapy during the four weeks prior to starting the con-

Table 1. Patient characteristics and baseline laboratory values. Transfusion requirement within four weeks prestudy (Percentage of patients transfused, mean volume of packed red blood cells [PRBC]).

	Control group (n = 88)	RhEPO group (n = 101)
Patient characteristics		
Sex		
Male	26 (30%)	23 (23%)
Female	62 (70%)	78 (77%)
Gynecological cancer	32 (36%)	36 (36%)
Breast cancer	22 (25%)	25 (25%)
Lung cancer	10 (11%)	9 (9%)
Urinary tract cancer	10 (11%)	10 (10%)
Gastrointestinal cancer	6 (7%)	12 (12%)
Other	8 (9%)	9 (9%)
Age (years)		
Median	56	53
Range	19–73	20–77
Weight (kg)		
Median	62	61
Range	41–110	43–103
Baseline hematology (median values)		
Hemoglobin (g/dl)	10.3	9.6
Hematocrit (%)	30.1	29.4
Reticulocytes (‰)	10.2	10.2
Platelets (10^9/l)	267	284
Leukocytes (10^9/l)	5.18	5.25
Neutrophils (10^9/l)	3.52	3.41
Transfusions within four weeks prestudy		
Patients transfused (%)	21.6	22.8
Volume of PRBC (mean)	133 ml	166 ml
Baseline EPO concentration	(n = 52)	(n = 72)
Median serum-EPO (mU/ml)	27.7	26.0
O/P ratio for serum-EPO	0.74	0.69
O/P ratio ≤ 0.9	40 (77%)	63 (83%)

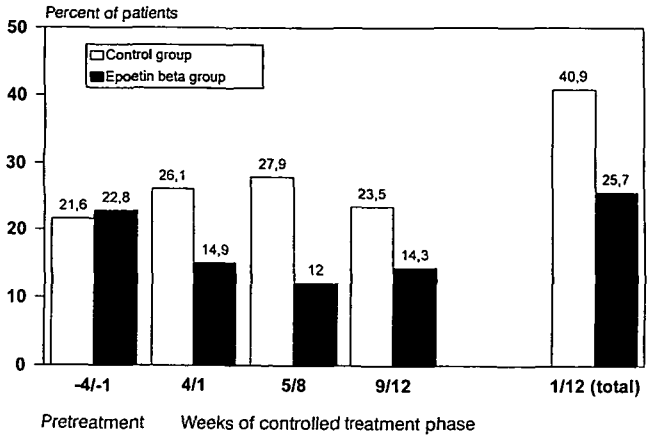

Figure 1. Percentage of patients with transfusions in the four-week intervals during the controlled treatment phase.

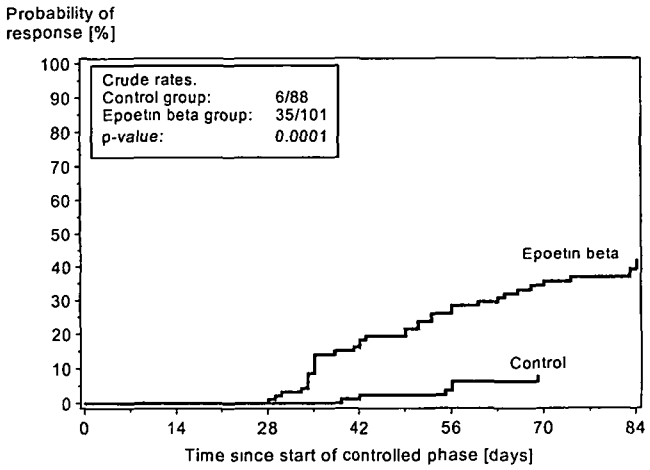

Figure 2. Time to response separated by treatment group using Kaplan–Meier estimation for the probability for response.

trolled treatment phase. Most of the patients were treated with combination chemotherapy. During the controlled treatment phase, more than half of the patients received platinum-based chemotherapy, 70 of them including cisplatin and 36 carboplatin. The distribution of increased doses of cisplatin or carboplatin at the beginning of the controlled treatment phase was balanced within the two treatment groups. Sixty-three percent of the patients received cisplatin at a dose level of > 75 mg/m^2/cycle and 72% received carboplatin at a dose level of > 250 mg/m^2/cycle.

As shown by the decreased neutrophil count (7% in both groups) there was an increased chemotherapy-induced depression of hematopoiesis during the controlled treatment phase as compared to baseline. Baseline hematological parameters, endogenous EPO production and prestudy transfusion requirement are summarized in Table 1.

Efficacy of rhEPO treatment

During the controlled treatment phase, the need for transfusions was reduced in patients treated with rhEPO but increased in control patients (Figure 1). This effect was most prominent in the second month of treatment (12% in the rhEPO group vs. 28% in the control group). The mean volume of PRBC transfused per four weeks was significantly lower in the rhEPO group (152 ml) than in the control group (190 ml, $P = 0.044$ in comparison to control).

The estimated probability of transfusion need within 12 weeks was 42% for the untreated controls and 28% for rhEPO-treated patients.

Response to treatment after 12 weeks of therapy was shown in 38% of rhEPO-treated patients, whereas only 9% of the untreated patients fulfilled the criteria for treatment response. The time to response according to treatment group is shown in Figure 2.

Analysis of prognostic factors for response

The subgroup analysis of various factors that may influence the need for blood transfusion and the effect of rhEPO treatment identified the type of chemotherapy and the administered dose level as predictive factors for the probability of response to rhEPO treatment. The need for transfusions was significantly lower (P = 0.0376) in the rhEPO group than in the control group in

Table 2. Number and percentage of patients with blood transfusions (BT) and response to rhEPO treatment in various subgroups during the controlled treatment phase.

Patients subgroup		Study arm	Patients with BT (%)	Life table rate for BT (%)[a]	Patients with response (%)	Life table rate for response (%)[a]
Type of chemotherapy	With platinum	rhEPO	14/57 (25)	26	23/57 (40)	50
		Control	22/51 (43)	45	4/51 (8)	9
	Without platinum	rhEPO	12/44 (27)	31	12/44 (27)	33
		Control	14/37 (38)	39	2/37 (5)	6
Platinum-containing chemotherapy	Low dose	rhEPO	5/28 (18)	18	11/28 (39)	41
		Control	8/26 (31)	31	2/26 (8)	8
	Increased dose	rhEPO	7/27 (26)	30	12/27 (44)	58
		Control	14/25 (56)	59	2/25 (9)	9
Type of tumor	Ovarian cancer	rhEPO	7/27 (26)	28	9/27 (33)	47
		Control	9/23 (39)	39	2/23 (9)	10
	Other tumors	rhEPO	19/74 (26)	28	26/74 (35)	41
		Control	27/65 (41)	42	4/65 (6)	7
Platinum-containing chemotherapy	Ovarian cancer	rhEPO	6/23 (26)	27	8/23 (35)	63
		Control	8/19 (42)	42	2/19 (10)	12
	Other tumors	rhEPO	8/34 (23)	25	15/34 (44)	48
		Control	14/32 (44)	45	2/32 (6)	7

[a] Life table rate for blood transfusions and response (Kaplan–Meier estimation) after 12 weeks of the controlled treatment phase. Median time to response and median time to first blood transfusion could not be estimated because of the limited study duration.

patients treated with platinum-based chemotherapy. In control patients receiving an increased dose of cisplatin (≥ 75 mg/m^2/cycle) or carboplatin (≥ 350 mg/m^2/cycle), the transfusion need was about twice as high as that in patients receiving lower doses (Table 2).

Subgroup analysis of patients receiving platinum-based chemotherapy was performed comparing patients with ovarian cancer vs. the combined subgroup including those with all other entities, due to the smaller number in these subgroups. In both groups of patients, rhEPO-treated patients demonstrated a need for transfusions lower by the same magnitude as compared to untreated controls. For the same subgroups a markedly higher response rate was seen in rhEPO-treated patients than in the control group (Table 2).

During the controlled treatment phase, the median Hb values measured at regular visits, irrespective of blood transfusions, increased gradually in rhEPO patients, whereas the median hemoglobin concentration in the control group remained unchanged. Two weeks after the beginning of rhEPO treatment the median hemoglobin concentration increased by 0.15 g/dl over that of the baseline value, whereas in the control group a decrease of hemoglobin concentration (−0.34 g/dl) was observed. This finding should be viewed against the background of frequency and volumes of transfusions, which were higher in the control group.

Analysis of endogenous EPO production demonstrated no correlation between EPO deficiency and response to rhEPO treatment for either an absolute EPO deficiency or for a baseline O/P ratio < 0.9. The same holds true for the subgroup of patients receiving platinum-based chemotherapy, where baseline EPO levels and O/P ratio were not predictive of the need for blood transfusions or treatment response. To obtain an adequate sample size in patients with platinum-based chemotherapy the cut-off point of the O/P ratio had to be changed to 0.8 for this subgroup (Table 3). These results have to be viewed against the background of the high proportion of patients in whom baseline EPO levels were not determined. Therefore, analysis of serum EPO levels and O/P ratio as a predictive factor for response to rhEPO treatment does not demonstrate reliable results, and has to be interpreted with caution.

Safety of rhEPO treatment

RhEPO was found to be safe and well tolerated both systemically and locally. None of the adverse events leading to death or withdrawal during the controlled treatment phase (14 deaths and seven withdrawals in 104 controls and eight deaths and 17 withdrawals in 114 rhEPO patients) were classified as being causally related to the study medication. Serious adverse events were reported for 30 of the 114 patients (26%) in the rhEPO group and 29 of the 104 control patients (28%). The nature and incidence of adverse experiences were similar in the two treatment groups.

Adverse events that were assessed as being possibly related to rhEPO therapy and that occurred during the controlled treatment phase included allergic reaction, hypertension, injection site pain, and rash (one patient each), as well as iron deficiency (four patients) and thrombocytopenia (two patients). There was no evidence of an effect of rhEPO therapy on blood pressure in patients in this study.

In addition, there were no trends toward clinically relevant changes in any of the safety laboratory variables

Table 3. Number and percentage of patients with blood transfusions (BT) and response to rhEPO-treatment dependent on serum EPO levels at baseline (≤ 50 vs. > 50 mU/ml) and ratio of observed vs. predicted serum EPO level (O/P ratio ≤ 0.9 vs. > 0.9).

			Patients with BT (%)	Life table rate for BT (%)[a]	Patients with response (%)	Life table rate for response (%)[a]
Serum EPO level at baseline (mUml)	≤ 50	rhEPO	10/60 (17)	19	24/60 (40)	46
		Control	7/36 (19)	21	1/36 (3)	3
	> 50	rhEPO	8/18 (44)	46	6/18 (33)	50
		Control	6/16 (38)	38	2/16 (13)	15
O/P ratio	≤ 0.9	rhEPO	11/63 (18)	20	25/63 (40)	46
		Control	9/40 (23)	23	1/40 (3)	3
	> 0.9	rhEPO	6/13 (46)	48	4/13 (31)	47
		Control	4/12 (33)	33	2/12 (17)	20
Platinum-containing chemotherapy	O/P ratio ≤ 0 8	rhEPO	7/31 (23)	25	14/31 (45)	55
		Control	7/22 (32)	34	1/22 (5)	5
	O/P ratio > 0.8	rhEPO	4/11 (36)	39	4/11 (36)	52
		Control	1/9 (11)	11	2/9 (22)	25

[a] Life table rates for blood transfusions and response to treatment (Kaplan–Meier estimation) after 12 weeks of the controlled treatment phase. Median time to response and median time to first BT could not be estimated because of the limited study duration.

in either of the groups. No antibodies against rhEPO developed during therapy in the study.

Discussion

The results of this open, randomized, controlled, parallel group study demonstrate that treatment with 5000 IU/day rhEPO s.c. leads to a reduction in the need for transfusions in patients with solid tumors during chemotherapy. The effect was particularly pronounced in patients receiving platinum-based chemotherapy. As expected from the underlying pathophysiological mechanisms of platinum-based chemotherapy in the development of anemia, there was no difference in rhEPO efficacy between ovarian cancer and other tumor types treated with platinum-containing chemotherapy. These results suggest that the effect of rhEPO is independent of solid tumor type with regard to its efficacy in preventing platinum-induced anemia.

The results of our study confirm those of several published studies in patients with various solid tumors treated with rhEPO. Such studies have consistently demonstrated that rhEPO treatment, independent of the underlying tumor type, leads to a significant reduction in the need for blood transfusions, and prevents a decrease in hemoglobin (thus preventing the development of anemia) or induces a considerable increase in hemoglobin [6, 11, 16].

In addition, our data show that the transfusion need is most pronounced in patients receiving increased doses of platinum-containing chemotherapy, in these patients rhEPO treatment may be particulary indicated.

Data from hemodialysis patients have shown that iron deficiency is one of the important factors leading to a reduction in the efficacy of rhEPO treatment [17]. At the end of the controlled treatment phase of our study, about half of the patients exhibited functional iron deficiency (transferrin saturation < 20%). To ensure that patients receive maximum benefit from rhEPO treatment, sufficient iron supplementation may be necessary [18, 19].

Although several clinical trials have demonstrated that rhEPO is an effective treatment in tumor- or chemotherapy-induced anemia, only a portion of patients respond to rhEPO therapy. As rhEPO treatment is expensive, it is important to determine a reliable means of predicting responders and nonresponders in these non-renal applications [10, 12, 20]. In our study, the relative EPO deficiency was not a predictive factor for response. Abels et al. report that endogenous erythropoietin levels are only a predictive factor in cancer patients without chemotherapeutic treatment. He found no statistically significant relationship between endogenous EPO concentration and response to rhEPO treatment in patients whose chemotherapy contained platinum and those whose CT did not [21]. The reasons for these findings are still unclear but may be related to the observation of temporarily increased levels of erythropoietin after administration of cyclic chemotherapy [22]. About 60% of our patients had received chemotherapy four weeks before the beginning of the controlled treatment phase. This may explain the negative relationship between endogenous EPO concentration and response in our study. On the other hand, our results could be biased by the high percentage of patients (31%) in whom baseline serum levels were not determined.

The analysis of various factors likely to be predictive of response (platelet counts, distant metastasis, previous blood transfusions, gender, transferrin saturation, investigational site location) demonstrate in almost all of the subgroups analyzed a marked reduction of blood transfusions and a higher rate of response in the epoetin beta-treated patients than in the control group. Due to the smaller sample sizes within the subgroups the differences between the treatment groups do not reach significant

values. Therefore, the interpretation of these results is not reliable.

In summary, the results of this randomized, controlled study demonstrate that rhEPO provides an effective, safe and well tolerated alternative treatment modality that can significantly delay or abolish the need for blood transfusions in patients with solid tumors and chemotherapy-induced anemia. However, the use of rhEPO-treatment is expensive. One week of rhEPO administration at a dose level of 450 IU/kg costs approximately $400. In contrast the estimated average direct costs of an allogenic unit of blood ranges from $150 to $422, representing the total costs of blood collection, disease testing, processing and inventory management, and compatibility testing [23].

Evaluation of cost-effectiveness in rhEPO therapy and blood transfusions has to be viewed against the background of two different treatment strategies. Blood transfusions are suitable for the immediate treatment of chemotherapy-induced anemia, especially if very low hemoglobin concentrations occur and the patient becomes symptomatic, but they provide only a short-term treatment effect and many patients require recurrent blood transfusions during chemotherapy. RhEPO therapy is effective for prevention and correction of chemotherapy-induced anemia, and compared to blood transfusions it can ensure continuous hemoglobin levels for a long treatment period. Because of these two different treatment strategies it is very difficult to evaluate the cost-effectiveness of rhEPO therapy, but an ongoing clinical trial was conducted to analyze the cost-effectiveness of rhEPO compared to blood transfusions.

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